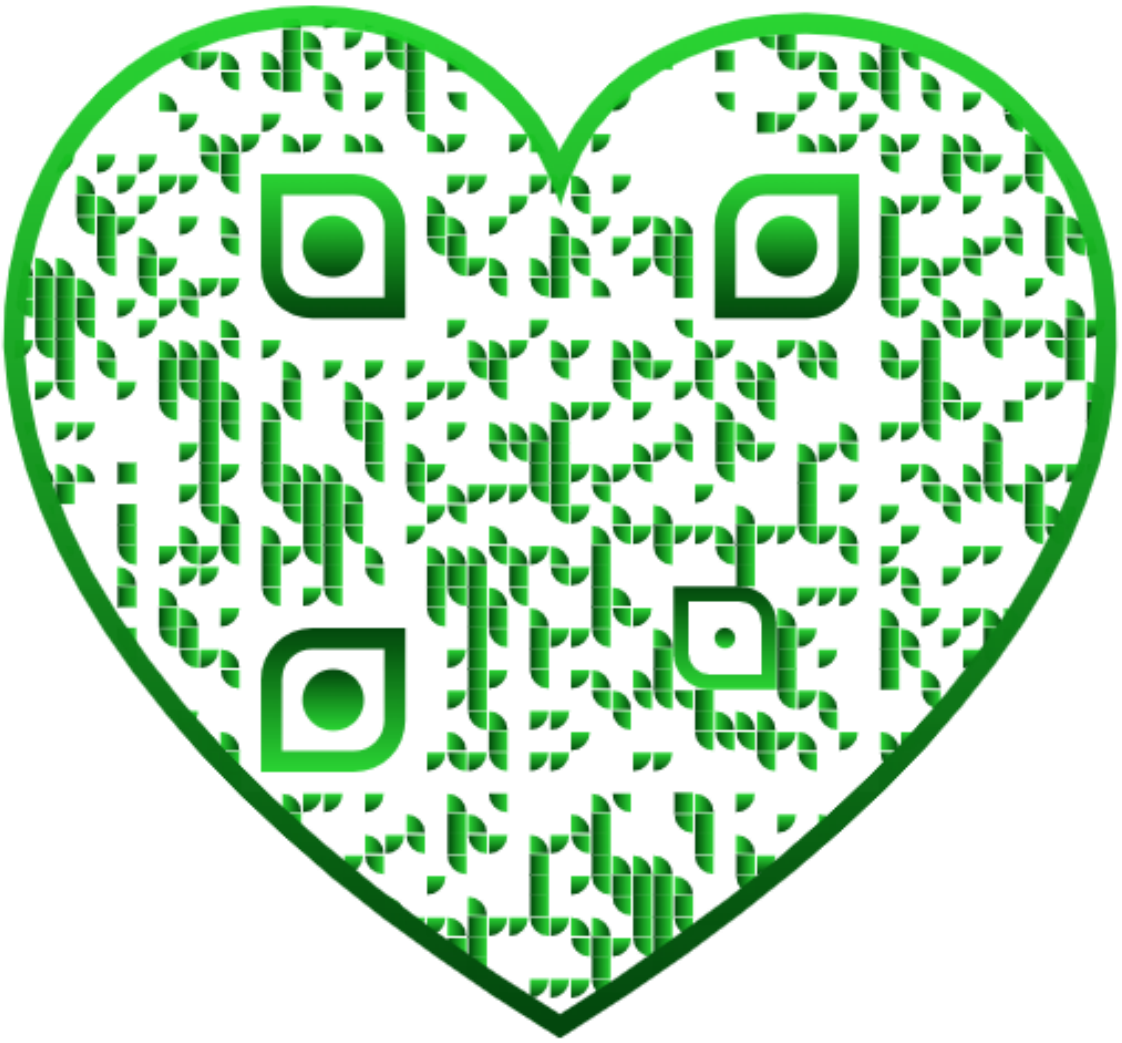
Ethiopian Food, Medicine and Healthcare Administration and Control Authority

Pharmaceutical Manufacturer GMP inspection Directive

January, 2017



Contents

Introduction 2
1. Short title 3
2. Definitions 3
3. Scope 4
4. Objective 5
5. Principles 5
6. Routine Inspection 6
7. Follow up Inspection 7
8. Sudden Inspection 7
9. Frequency of inspection 7
10. Role and Responsibility of GMP inspector 8
11. Role and Responsibility of GMP lead Inspector 8
12. Profession, Qualification and Competency of GMP Inspector 9
13. Assignment of Inspector 10
14. Code of conduct of Inspectors 11
15. Application procedure 11
16. Program Administration and Management 12
17. General 12
18. Classification and Recommendation of Observation 12
19. Inspection Report Writing, Reviewing and Approval Process 13
20. Inspection Quality Assurance 14
21. Inspector 14
22. Manufacturer 15
23. Complaint related to assignment of inspector 15
24. Complaint over disciplinary measure on inspector 16
25. Complaint related to inspection finding and decision 16
26. Service Fee 17
27. Inapplicable laws 17
28. Effective date 17
ANNEX 1 18

Introduction

WHEREAS, ensuring Compliance with the current Good manufacturing practice of pharmaceutical products is necessary condition for pre and post approval of Marketing Authorization;

WHEREAS, it is necessary to ensure products are consistently produced and controlled according to quality standards appropriate to their intended use and as required by the product specification;

WHEREAS, it is necessary to utilize only highly qualified Expertise for the foreign & local GMP inspection program who have extensive experience in conducting Pharmaceutical Quality Assessment, Quality Assurance and Pharmaceutical inspections with demonstrated track records of working effectively in a tight time frame and under considerable pressure;

WHEREAS, considering the resource-intensive nature of the foreign GMP inspection and the current focus of the Government on local manufacturers, it has become clear that effective and efficient inspectional coverage is crucial to the successful management of the program and that can be achieved only through maintenance of consistency and uniformity of inspection and enforcement activities.

WHEREAS, it has become increasingly evident that a formal guidance is necessary to address the issues specific to the foreign and local drug inspection operations as the Authority needs to broaden the group of personnel to meet the objective of the program and through this directive, the Authority strives to ensure that it continues to realize the consistency and the uniformity in the overall inspectional/enforcement activities;

NOW, THEREFORE, this directive is issued in accordance with Article 55 (3) of the Food, Medicine and Healthcare Administration and Control Proclamation No.661/2009 and Article 98 of the Food, Medicine and Healthcare Administration and Control Regulation no 299/ 2013.

PART ONE

GENERAL

1. Short title

This directive may be cited as "Pharmaceutical Manufacturer GMP Inspection Directive No. 338/2020

2. Definitions

In this directive, unless the context otherwise requires:

1) "Applicant" means the person or entity who submits a GMP inspection application to the Authority, and responsible for information provided in the application;
2) "Manufacture" means all operations of purchase of materials and products, production, quality control, packaging, repackaging, labeling, relabeling, release, storage and distribution of pharmaceutical products, and the related controls;
3) "Manufacturer" means a company that carries out operations listed under Article 2 sub-article (4) of this directive;
4) "Good Manufacturing Practice (GMP)" means a part of quality assurance which ensures medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing Authorization or product specification;
5) "Marketing Authorization" means an official document issued for the purpose of marketing or free distribution of a product after evaluation of safety, efficacy and quality of the product;
6) "Pharmaceuticals" means any substance or mixture of substances that may be used in or administered to human being either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;

7) "Stringent Regulatory Authority" means a regulatory Authority that has international recognition and stringent regulatory requirement, practices and trend past history for registration of pharmaceuticals and site GMP Inspection;
8) "conflict of interest (COI) " means a situation in which a person or an organization is involved in multiple interests, financial or otherwise, one of which could possibly corrupt the motivation or decision-making of that individual or organization and has the potential to influence or compromise professional decision making in regulatory service or any other professional activity;
9) "GMP inspector" means a person who is appointed by the Authority as an Auditor or assessor in order to verify cGMP compliance of a manufacturing site;
10) "Lead GMP inspector" means GMP inspector who fulfills the requirement of lead GMP inspector and assigned with the responsibility of leading a GMP inspection team carrying out inspection of a specified Pharmaceutical manufacturing site;
11) "Authority" means the "Ethiopian Food, Medicine and Health Care Administration and Control Authority;
12) Any expression in the masculine gender shall also apply to the feminine gender.

3. Scope

1) This Directive shall be applicable on all local and Foreign Finished Pharmaceutical Manufacturing plants.
2) Notwithstanding sub-article (1) of this article, GMP inspections for Active Pharmaceutical Ingredients manufacturing plants shall not be covered by this directive.

4. Objective

The objectives of this directive shall be:

1) To set legal binding framework on how the Authority is currently conducting GMP Inspection and to overcome the existing problems associated with the inspection activities;
2) To provide specific direction on how to accept and process applications, address logistical issues, and handle compliant on an inspection to be carried out on both local and foreign establishments.
3) To provide specific direction on Assignment of inspectors, Report writing, Classification of findings, Recommendation and to assure transparency and accountability of inspectors.

5. Principles

1) Pharmaceutical Manufacturing site shall only be visited or registered, if it has been licensed to manufacture medicines by the licensing Authority of the country of origin and it has continued production and marketing of its products continuously in the country of origin for a period of not less than three years.
2) Both local and foreign manufacturers of pharmaceutical shall only be registered if the Authority is convinced by compliance of the manufacturing site with the current Good Manufacturing Practice in the production of Pharmaceutical and Biological products, unless otherwise justified.
3) All finished pharmaceutical facilities shall be subjected to site GMP Inspection once every Five years, unless otherwise notified.
4) Site GMP Inspection shall be carried out after Dossier Evaluation is completed (New and/or Re).
5) Facilities located in countries with stringent NMRAs and WHO prequalified product shall be subjected to document review, unless otherwise required. However, whenever necessary, onsite inspection may be carried out.

6) Whenever necessary, GMP inspection shall be carried out with mutual recognition with identified and selected Regulatory Authorities. The Authority shall accept GMP Inspection report from these regulatory Authorities with pre agreed preconditions.
7) In response to the application submitted for the inspection of Pharmaceutical manufacturer production sites a 3 member inspection team shall be assigned.
8) All production lines shall be running a major processing activity during the inspection to enable the team to evaluate their performance.
9) Two days or more shall be allocated for the inspection of each manufacturing site depending on the lines available and only on site Inspection shall be carried out where payment is effective.
10) GMP inspection shall be carried out using Ethiopian National GMP Guideline and/or the World Health Organization (WHO) GMP Guideline.
11) GMP task force shall be organized and members shall be assigned by the Authority.

PART TWO

Type and Frequency of Inspection

6. Routine Inspection

1) Routine inspection shall be a full review of all aspects and components of GMP within a facility.
2) Routine inspection shall be conducted under an announcement when a newly established manufacturing facility or a manufacturer who has expressed interest of expanding manufacturing activities including, introduction of new products, modification of manufacturing methods or processes; or changes in key personnel, premises and/or equipment and When GMP certification has expired within 5 years.

7. Follow up Inspection

1) Follow up inspection shall be conducted specifically to monitor the result of corrective actions of the manufacturer following a previous inspection.
2) Depending on the nature of the defects and the work required, follow-up inspection shall be carried out within reasonable time after the previous inspection.
3) Follow-up inspection shall be limited to specified GMP non compliances that have been observed if the inspection is carried out within 6 months after receiving official inspection reports, otherwise a full inspection shall be initiated.
4) Notwithstanding Sub-article (3) of this article, depending on pre agreement process due to the nature of the previous observation at submitted corrective and preventive action (CAPA), the framed time may be longer than 6 months after receiving official inspection reports.
5) Any applicant shall apply only for two round follow up inspection.

8. Sudden Inspection

1) A sudden inspection shall be undertaken to do spot checks which could focus on one product, a group of related products, or a specific operation.
2) A sudden inspection shall be conducted when there are complaints about a specific product that suggest a defect, when there is a product recall due to adverse drug reaction, Post Market Surveillance, to gather specific information, or to investigate specific operations of the manufacturing processes and it shall not be announced.

9. Frequency of inspection

1) Mmanufacturers sites shall be inspected once every 5 year for the purpose of registration of their products.
2) Without prejudice to sub-article (1) of this article, depending on the type of inspection to be performed Manufacturers may be inspected more than once in a 5 year period.

PART THREE

Role, Responsibility, Qualification and Assignment of GMP Inspector

10.Role and Responsibility of GMP inspector

1) GMP inspector shall prepare and get ready before undertaking a GMP inspection.
2) GMP inspector shall behave in an ethical manner and do the task assigned to him/her by the lead GMP inspector.
3) GMP inspector shall inspect a facility in a professionally oriented practice and team focus.
4) GMP inspector shall report the findings and recommendations of the inspection within the agreed time.
5) GMP inspector shall evaluate his/her daily activity performance and get prepared for the next inspection.

11. Role and Responsibility of GMP lead Inspector

1) GMP lead inspector shall effectively and efficiently lead members of the inspection team and shall discuss on what to do, extrapolate and forecast possible areas of the facility needs, aiming to maximize efficient gains of the actual inspection**.**
2) GMP lead inspector shall Prepare for and organize preparation for inspection with the help of mock audit, if possible**.**
3) GMP lead inspector shall act as a liaison to communicate responsible contact person of the facility and assure all logistics are finalized before travelling.
4) GMP lead inspector shall ensure the integrity and behavior of the inspection team.
5) GMP lead inspector shall ensure inspection is carried out based on the direction given from responsible Directorate of the Authority.
6) GMP lead inspector shall report the findings and recommendations of the inspection within the agreed time.
7) GMP lead inspector shall present a detailed factual report on the manufactured goods and control of the manufacturer inspected and the report shall reflect the

observations on the standards of manufacturer and control applied to specific products.

8) GMP lead inspector shall evaluate the overall performance of the team members and Propose possible solution for any problem which arises during the inspection time.
9) GMP lead inspector and the inspection team as a whole shall respect cultural integrity of the country where the facility is situated.
10) GMP lead inspector shall evaluate daily performance of the inspection team and shall undertake the required preparation for the next inspection.

12. Profession, Qualification and Competency of GMP Inspector

1) All assigned inspectors shall be pharmacists in profession. However, other professionals (chemist, microbiologist and biologist) with acceptable qualification and competency might be assigned whenever necessary.
2) All Inspectors shall be qualified to be nominated as inspector and have to take advanced GMP training and examination organized by the responsible body. The potential nominee shall pass the evaluation examination with a minimum passing mark of 70 and each potential nominee shall take evaluation examination at least once in two years.
3) Lead inspector shall have specific specialization in Pharmaceutics or Pharmaceutical analysis and Quality Assurance or Industrial Pharmacy or Pharmaceutical Microbiology or Pharmacology having at least 2 round inspection experience as inspector. However, whenever necessary, pharmacists or professionals from other related disciplines having 3 round inspection experience as an inspector shall be assigned as lead inspector.
4) Licensed, certified and accredited inspector shall be assigned as inspector and lead inspector as top priority.
5) The Authority shall give recognition to those inspectors who participate in, at least 6 rounds, inspection of Foreign Pharmaceutical Manufacturers for the purpose of registration, follow-up and investigation with history of excellent conduct and professional talent.

13. Assignment of Inspector

1) Experts having a minimum of 3 years experience in Regulatory functions with the required qualification, training and competency shall be given priority to be assigned as GMP inspector.
2) Without prejudice to the preceding sub-article of this article, if it is deemed to be necessary, experts having a minimum of 6 years experience of working in Prequalified and/or GMP Complied Manufacturing Facilities of Production and Quality Assurance department may be assigned.
3) Experts having a minimum of 6 years experience in Regulatory functions at Dossier Evaluation, Medicine Quality Control Laboratory and Medicine Facility Inspection; and having the required qualification, training and competency shall be given priority to be assigned as Lead inspector.
4) Without prejudice to sub-article (3) of this article , if it deemed necessary, experts having a minimum of 10 years experience of working in Prequalified and/ or GMP Complied Manufacturing facilities of Production and Quality Assurance department may be assigned.
5) International experts from World Health organization (WHO), PIC's, EMA and other organizations having the required qualification, experience and competency as per the above stated provisions shall be assigned as lead inspector whenever necessary.
6) Whenever required, GMP Inspection shall be carried out with mutual recognition with identified and selected Regulatory Authorities. The Authority shall accept GMP Inspection report from these regulatory Authorities with pre agreed preconditions.
7) Expert working as promoter, regulatory functions expert in local agents and on other related areas which are deemed to have conflict of interest with the inspection shall not be nominated as inspector and lead inspector.

14. Code of conduct of Inspectors

1) Inspectors shall strive to achieve the highest ethical and performance standard in carrying out the inspection activities, and shall conduct the inspection with National Integrity.
2) Inspectors shall uphold the honor and dignity of a GMP Inspector and avoid association with any enterprise of questionable character or apparent conflict of interest.
3) Any assigned inspector shall not use his/her position for personal gain, and he/she inspectors shall not receive presents in any form.
4) Inspectors shall conduct inspection in a manner that will assure independence from outside influence and interest that would result in compromise of his ability to render a fair and impartial opinion regarding the inspection conducted.
5) Inspectors shall Maintain personal hygiene and dress in respectable attire in accordance with acceptable norms.

PART FOUR

Procedural Provisions

Section-One

Application and program Administration

15. Application procedure

1) Local licensed agent, in cases of foreign facilities and local manufacturing facilities shall submit a written application for inspection to responsible Directorate of the Authority.
2) All correspondence and documents required to be submitted shall be in English, and if the document required is not in English, it should be accompanied by a certified translation.

16. Program Administration and Management

1) Both the local and foreign inspection program shall be managed and directed by responsible and / delegated Directorate, and the Directorate shall schedule all the inspection trips and provide all the resources necessary for the program activities (like Site master file and others).
2) Inspectors and Lead Inspectors shall be nominated by responsible and/or delegated Directorate of the Authority or entity under the requirements of this directive and appointed by Deputy Director General of Inspection and Licensing of the Authority.
3) Responsible and delegated Nominating Directorate of the Authority shall ensure in advance the presence of any conflict of interest among the assigned inspectors.

Section-Two
Inspection Method and Procedure

17.General

1) Earliest inspection application shall be given priority during inspection planning or scheduling.
2) Without prejudice to sub-article (1) of this article, sites whose inspection would be crucial in making an ongoing regulatory decision or meeting an emergency or a public health issue shall be given priority during Inspection planning,
3) Based on the type of inspection and type of manufacturing site (SRA approved or none approved), inspection shall be carried out onsite or it shall be prevail desk top review.

18.Classification and Recommendation of Observation

1) Situations involving fraud, misrepresentation or falsification of source data or records linked with pharmaceutical manufacturing shall result in a non-compliance rating.

2) Non-compliance should be noted by Inspectors and classified as critical, major and minor.
3) Manufacturer with non compliance even with single critical finding shall be refused from acceptance for registration. If five and more major findings are found in five critical areas of manufacturing facilities (Production, Quality Control, Water system, HVAC, Documentation and others) are observed, manufacturer shall be refused from acceptance from registration.
4) Corrective and Preventive measures taken by the Manufacturer shall be submitted to the Authority within 15 working days after receiving formal report for Non compliance of Minor and Major observations.

19. Inspection Report Writing, Reviewing and Approval Process

1) Inspection report shall be written immediately on each day after completing the inspection according to Standard Operating Procedures for preparing and reviewing GMP Inspection Report.
2) The compiled report shall be submitted to responsible and /delegated Directorate within 14 calendar days upon completion of inspection.
3) Responsible and /delegated Directorate of the Authority shall distribute the report for reviewing process to GMP task force within 3 working days upon receipt from the team. The Task force shall review the report within 5 days of receipt.
4) Responsible and /delegated Directorate of the Authority shall make sure that the GMP inspection report is sent to the inspected facility within 30 calendar days after receiving the inspection report.
5) The Inspection report shall be provided with sufficient details in order to allow an independent assessment, comprehension and easy decision making.
6) Observations that are considered to be inconsistent with GMP requirements shall be listed and cross referenced. Where observations are included in the report, clear distinction shall be made between “compliances” and “non-compliances”, and Non-compliance observations shall be classified as “critical”, “major” and “minor”.

20. Inspection Quality Assurance

1) The inspection activities shall be supervised with Senior Technical Managers of the Authority whenever necessary. Moreover, Senior Technical Managers shall be involved in follow up inspection to clear complain, proposing future strategies and promoting overall regulatory activities.
2) Whenever necessary, external Auditors shall be involved in identifying frauds, corruptions/bribes and other misbehaving activities which are suspected in having positive and negative impacts on decisions made.
3) Trend Reports of successive Inspection Report shall be statistically evaluated and consumed for further regulatory measures.
4) The GMP Task force shall arrange internal capacity building program, evaluation of inspector and propose different strategies.

PART FIVE

Administrative Measure and Compliant Handling Procedure

Section-One

Administrative Measure

21. Inspector

1) If, through the inspection, a minor offence including, failure to report on timeline, disturbing team spirit, inability to hide individual manufacturer confidential information and related offences are commuted, and if the offender admits and honestly reports the offence to the Authority that he or she committed the offence and if the Authority decides that the offence had no relation with the final inspection findings decision, he or she shall be subjected to educational measures and a warning. However, if similar behavior is observed for the second time it will result in Disciplinary measures.

2) If, through the inspection, a major offence related to corruption and related issues is found and the Authority believes or has a reason to believe that the offence had clear negative impact on final inspection findings decision, he/she shall be subjected to imposition of the following Disciplinary measures;
    a) Be criticized and admonished by the recording of a note in his/her biographical file;
    b) Be suspended from receiving any promotion, or reward;
    c) Be suspended from future nomination as an inspector; or
    d) Be subjected to case proceeding before a responsible team of the Authority structured for hearing and giving a response to this kind of offences.

22. Manufacturer

1) A manufacturer inspected for two consecutive inspections and failed to comply with the requirements shall be subjected to suspension for two years.
2) Any manufacturer who tries to corrupt or deceive the inspectors shall be subjected to suspension for two years.
3) A manufacturer who fails to dully arrange, prepare or facilitate the inspection process according to the directive or who became absent during the inspection shall be suspended for one year.
4) A manufacturer who shows or tries to show a facility other than the site where, the Authority review located on site master file is subjected to suspension for two years.

Section-Two
Complaint Handling Procedure

23. Complaint related to assignment of inspector

1) Any potential candidates may appeal against assignment of inspectors for GMP Inspection to Deputy Director General of Inspection and Licensing Directorate and/or responsible team of the Authority structured for hearing and giving a response to this kind of appeal.

2) The compliant prepared in accordance with sub-article (1) of this article shall be in written form and may also provide appropriate documentary evidence and other evidences relevant to the case.
3) Where the compliant fulfills the above stated requirements, the appropriate body of the Authority shall receive the compliant and shall notify its final decision to the complainant within 2 days from the receipt of the compliant.
4) The response to the compliant prepared in accordance with sub-article(3) of this article shall , at least, include the reason why the compliant should not be acceptable for any reasonable ground.

24. Complaint over disciplinary measure on inspector

Any inspector who has compliant against a disciplinary measure taken as per Art. 21 of this directive shall bring his/her compliant to the appropriate body of the Authority and the appropriate body of the authority shall notify its decision within 15 days from the receipt of the compliant.

25.Complaint related to inspection finding and decision

1) Any manufacturer may appeal against any decision of the Authority. Appealing period shall not be more than 30 days from the receipt of official letter from the Authority.
2) Any manufacturer may appeal against any decision of the Authority. Appealing period shall not be more than 30 days from the receipt of official letter from the Authority.
3) The compliant prepared in accordance with sub-article (1) of this article shall, at least state, the Authorities' alleged reason to take the measure, decision of the Authority, reasons of the complainant why he/she believes the measure is unjustifiable or inappropriate , and shall be signed and dated by the complainant.
4) The compliant prepared in accordance with sub-article (1) of this article shall be in written form and may also provide appropriate documentary evidence and other evidences relevant to the case.

5) Where the compliant fulfills the above stated requirements, the appropriate body of the Authority shall receive the compliant and shall notify its final decision to the complainant within 15 days from the receipt of the compliant.
6) The response to the compliant prepared in accordance with sub-article(4) of this article shall , at least, include the reason why it is legal to take the challenged measure and why the compliant should not be acceptable for any reasonable ground.

PART SIX
Miscellaneous

26. Service Fee

Any person who seeks regulatory service under this directive may be required to pay applicable service in accordance with Regulation No.370/2015.

27. Inapplicable laws

Any customary practice which is inconsistent with this directive shall not be applicable with respect to those matters provided for in this directive.

28. Effective date

This directive shall enter into force on the date of 1 September, 2017.

Yehulu Denekew

Director General
Ethiopian Food, Medicine and Healthcare administration and Control Authority

ANNEX 1

Foreign GMP Inspection application form

Part A- Applicant information			
Date of Applications			
Name of Applicant			
Name of Product Registration Holder			
Addres s			
Company/ Business Registration No. (Of the Agent)			
Tel. No			
Email address		Fax No	
Part B- Foreign manufacturer information			
Manufacturer			
Address			
Country			
Purpose of application	*Tick the column behind*		
		Product registration (New)	
		Product registration/ (renewal)	
		Change of manufacturing site	
		Others (please specify)……	

Part C scope of inspection

Select pharmaceutical dosage forms to be inspected (tick the column in front of the dosage form)

Large volume parenterals		Tablet	
Small volume parenterals		Capsule	
Liquid (external)		powder	
Liquid (internal)		Granule	
Cream		Ointment	
Lotion			

Others (please state)……
……
……

State any of the following product that are to be included in the inspection

Penicillin	
Cephalosporin	
Cytotoxic or anticancer preparation	
Biologicals(vaccine, blood products, biotechnology products)	
Hormones	
Steroids	
None of the above	

Part-D List of supporting documents (please ensure that the following documents are attached together with this application		
	Yes	Not applicable
A copy of company /business registration (for the agent in Ethiopia)		
Details of new product to be registered in Ethiopia (annex I)		
Details of existing registered product for renewal of product registration (Annex II)		
Details of existing registered product for change of manufacturing site		
Site master file		
Validation master plan		

Part E application declaration

1. I am here by authorized by the company to make this application
2. I have read and understood the content of GMP guidelines and registration guidelines of EFMHACA
3. I declare that the particulars given this application and the supporting documents are true or authentic or true copies and undertake to notify to EFMHACA within one week of any change in the particulars submitted in this application
4. I hereby confirm that I agree with any decision from EFMHACA Regarding this application

Full name ……..

Designation…….

Signature ……

Stamp

For Official Use only

Application No…….

Name and signature of Officer processing this application

……

……